REMARKS

Applicants have amended the claims in order to more precisely define the scope of the invention and to address the §112 rejections found in the outstanding Official Action. Generally, Applicants have amended the claims to correct those grammatical errors identified by the Examiner in the Official Action. Claim 1 has been amended to recite at least a fragment of a tumor-associated gene and at least a fragment of a cytokine gene. Claim 2 has been amended to remove the term "expression" in order to make it clear that a mammalian promoter is claimed. Claim 3 has been amended to clarify that promoters of CMV, PSV or LTR are claimed.

With respect to the §112 rejection of claims 9 and 16 for not having a hyphen, Applicants assert that the claims as originally filed recite "N'-neu". Claim 11 has been amended to replace the term "mature" with the term "full length". Claim 12 has been amended so as to be grammatically correct. Claim 15 has been amended to depend from claim 4 so as to provide antecedent basis for the recitation of "said IRES segment". Support for all these amendments, where necessary, may be found throughout the Specification as originally filed.

With respect to the rejection of claims 9 and 16 under 35 U.S.C. §112 as being vague in the recitation of the term "N'-neu gene," Applicants enclose herewith a reference paper entitled "Therapeutic HER2/Neu DNA Vaccine Inhibits Mouse Tumor Naturally Overexpressing Endogenous Neu" and provide the following comments.

Neu is a transmembrane protein containing extracellular, transmembrane, intercellular domain (please refer to the enclosed reference paper, p.290 (Introduction)). The definition of N'-neu (please refer to the enclosed reference paper, p291 (Results, Construction and Charaterization of N'-neu-cytokine fusion genes)) is the N'-extracellular portion of neu, which contains amino acids 1-650 in rats, humans and mice. The N'-neu in DNA vaccine can be exposed on the surface of cancer cells and then activates antibody response. Applicants are the first ones to

prove that N'-neu DNA vaccine has cancer therapeutic effect rather than just a prophylactic effect (please refer to the enclosed reference paper , p.291, left column, "our results demonstrated the rat N'-neu DNA vaccine inhibited the progression of established tumor,....."). This discovery is vastly different from the prior art, which only demonstrates the effect of DNA vaccine in preventing the establishment of tumors.

In light of these corrections, Applicants respectfully assert that all claims currently pending in the application are now in full compliance with the requirements of §112.

Applicants have also submitted herewith a substitute specification as required by the Examiner in the outstanding Official Action. Applicants have made every effort to correct all grammatical and typographical errors found in the originally filed Specification. No new matter is introduced in the substitute Specification.

The rejection of claims 1-3, 5, 8, 10, 12, 13 and 18 under 35 U.S.C. §102(b) as being anticipated by Pasquini has been carefully considered but is most respectfully traversed in light of the amendments to the claims and the following comments.

Applicants wish to direct the Examiner's attention to MPEP § 2131 which states that to anticipate a claim, the reference must teach every element of the claim.

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed.Cir. 1990).

The presently amended claims are drawn to a DNA vaccine comprising at

least a fragment of a tumor-associated gene and at least a fragment of a cytokine gene. The tumor-associated gene and the cytokine gene are incorporated into a vector having a suitable promoter or a translation regulatory sequence. The promoter may be a CMV promoter, a PSV promoter or a LTR promoter. The cytokine gene may be a full length gene segment of Interleukin-2. The tumor-associated gene may be an N'-neu gene. The tumor-associated gene and the cytokine gene are expressed simultaneously in fusion form or expressed respectively with separated promoters or translation regulation factors. As discussed throughout the Specification, the DNA vaccine disclosed in the present application is directed to inhibiting or retarding the growth of tumors.

Pasquini, on the other hand, discloses two vaccines against pre-B cell leukemia, one of which expresses CDR_2-CDR_3 specific IgH as a fusion product with mouse GM-CSF. T and B cell malignancies express rearranged antigen receptors that are unique to the tumor. As a result, Pasquini teaches vaccines expressing a fusion polypeptide between mGM-CSF, raising the immune response to an idiotype DNA vaccine targeting a B cell lymphoma, and an IgH CDR derived form a pre-B leukemia cell line that can protect mice against a leukemia challenge. This demonstrates the feasibility of immunizing against a malignant cell-specific intracellular antigen.

The purpose of the vaccine disclosed in Pasquini is to cure B cell malignancies. To the contrary, the present invention is aimed at treating lung cancer, breast cancer, ovarian cancer or bladder cancer. Due to the different treating targets, the DNA vaccine strategies of each vaccine are distinctive. Pasquini manufactures DNA vaccine that expresses anti-CDR_2-CDR_3 IgH and mM-CSF. However, the present invention discloses DNA vaccine combining N'-neu and IL-2. Therefore, Pasquini does not anticipate the DNA vaccine of the present invention. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 1-3, 5, 8, 10-12 and 14 under 35 U.S.C. §102(b) as being anticipated by Glorioso has been carefully considered but is most respectfully

traversed in light of the amendments to the claims and the following comments.

Amended claim 14 of the present application recites that the tumor-associated gene and the cytokine gene are constructed in such a way that they are two independent genes controlled respectively by two independent promoters.

Glorioso discloses a method of preparing HSV multigene expression vectors which comprises co-transfecting a source vector and a mutating cassette together into a population of appropriate host cells such that homologous recombination occurs between the mutating cassette and the source vector whereby the mutating cassette replaces a region of the HSV genome. Although Glorioso discloses that IL-2 was used for manipulating HSV expression vector, Glorioso does not disclose applying the vector to treat any cancer animal model nor does it demonstrate the effect of the HSV expression vectors carrying IL-2. Furthermore, Glorioso fails to disclose that the HSV vector can be used us DNA vaccine. To the contrary, the DNA vaccine of the present invention comprises IL-2 and N'-neu gene and is intramuscularly administered into the tumor site. The Specification of the present application demonstrates the remarkable effect of suppressing tumor growth and prolonging the lifetime of mice. Therefore, Glorioso does not anticipate the DNA vaccine of the present invention. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 1-5, 8, 12, 14-15, 17 and 18 under 35 U.S.C. §102(e) as being anticipated by Cotten has been carefully considered but is most respectfully traversed in light of the amendments to the claims and the following comments.

The amended claims recite in part that the DNA vaccine contains an IRES element and that the tumor-associated gene and the cytokine gene are two separate genes regulated by a promoter and IRES element.

Cotten discloses a recombinant CELO virus or CELO virus DNA comprising a CELO wild type genome containing at least one deletion, which consists of nucleotides 37, 391-97,972 of the CELO wild type virus genome. The deletion will result in a complete loss of Gam1 expression or prevent the expression of a

functional Gam1 protein that inhibits replication capacity of CELO virus. The purpose of the invention disclosed in Cotten is to create an alternative adenovirus vector for use as a gene delivery vector. No portion of Cotten discloses applying recombinant CELO virus to treat lung cancer, breast cancer, ovarian cancer or bladder cancer with IL-2 and N'-neu as disclosed in the present application. Although Cotton recites that the recombinant CELO virus can be applied to gene therapy and as tumor vaccine, Applicants respectfully assert that this is not adequate support for the contention that Cotten anticipates the present invention. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 6, 7 and 9 under 35 U.S.C. §103(a) as being unpatentable over Glorioso or Cotten in view of Hand-Zimmerman has been carefully considered but is most respectfully traversed in light of the amendments to the claims and the following comments.

Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending

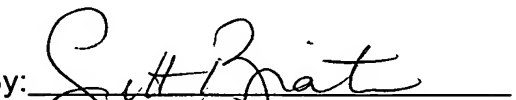
therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Hand-Zimmermann discloses that HER-2/neu (pl85) is the protein product of the HER-2/neu oncogene. The HER-2/neu gene is amplified and the HER-2/neu protein is overexpressed in a variety of cancers including breast, ovarian, colon, lung, prostate and hematological cancers.

Glorioso fails to teach applying the vector disclosed therein to treat any cancer animal model. Moreover, Cotton aims to create an alternative adenovirus vector for use as a gene delivery vector. There is no disclosure in Cotten of applying recombinant CELO virus to treat lung cancer, breast cancer, ovarian cancer or bladder cancer with IL-2 or N'-neu. According to MPEP 2141.01(a), an obviousness rejection combining two or more references must use references from analogous arts. Neither Cotten nor Glorioso are analogous art to the present invention, which discloses a DNA vaccine combining IL-2 and N'-neu to treat solid tumors. Therefore, an obviousness rejection based on combination of references including Glorioso, Cotton and Hand-Zimmermann to disclose or suggest a DNA vaccine combining IL-2 and N'-neu to treat cancer as claimed in the present application is improper. Because the Official Action has failed to make out a proper *prima facie* case of obviousness as required by MPEP 2143, Applicants respectfully request that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

BACON & THOMAS, PLLC

By: 
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